Common Implementation Strategy for the Water Framework Directive

Environmental Quality Standards (EQS)

Substance Data Sheet

Priority Substance No. 25

Octylphenols (para-tert-octylphenol)

CAS-No. 1806-26-4 and 140-66-9

Final version
Brussels, 31 July 2005

Disclaimer

This data sheet provides background information on the setting of the Environmental Quality Standard in accordance with Article 16 of the Water Framework Directive (2000/60/EC). The information was compiled, evaluated and used as outlined in the Manual [4] and has been discussed in a consultative process with the Expert Advisory Forum on Priority Substances and the Expert Group on Quality Standards. Furthermore, it has been peer-reviewed by the SCTEE [16]. The substance data sheet may, however, not necessarily represent the views of the European Commission.

New upcoming information was considered and included up to the date of finalisation of this data sheet. Information becoming available after finalisation of this document will be evaluated in the review process of priority substances according to Art. 16(4) of the Water Framework Directive. If necessary, the Environmental Quality Standard substance data sheets will then be revised in the light of technical and scientific progress.

1 Identity of substance

Priority Substance No: 25	Octylphenols (para-tert-octylphenol)
CAS-Number:	1806-26-4 (140-66-9)
Classification WFD Priority List *:	PSR

* PS: priority substance; PHS: priority hazardous substance; PSR: priority substance under review; OSC: other substance of concern

2 Proposed quality standards

2.1 Overall quality standards

Ecosystem	Quality Standard	Quality Standard "rounded value"	Comment
AA-QS inland surface waters	0.122 µg/l	**0.12 µg/l**	protection of the pelagic community, precautionary value targeted to prevent the occurrence of endocrine effects; see section 8.1
AA-QS other surface waters covered by the WFD	0.0122 µg/l	**0.012 µg/l**	protection of the pelagic community; see section 8.1
MAC-QS (ECO)	0.133 µg/l	**0.13 µg/l**	see section 8.1

2.2 Specific quality standards

Protection Objective	Quality Standard	Comment
Pelagic community (freshwater)	0.122 µg/l	see section 8.1
Pelagic community (saltwater)	0.0122 µg/l	see section 8.1
Benthic community (freshwater sediment)	7.4 µg/kg wet wt 34 µg/kg dry wt	tentative values derived by EP method; see 8.2
Benthic community (saltwater sediment)	0.74 µg/kg wet wt 3.4 µg/kg dry wt	tentative values derived by EP method; see 8.2
Predators (second. poisoning)	10 mg/kg food (wet weight) corresponding conc. in water: 15.8 µg/l	see 8.3
Food uptake by man	8.7 mg/kg fishery product (wet weight) corresponding conc. in water: 13.7 µg/l	see 8.4
Abstraction of water intended for human consumption (AWIHC)	No EU DW abstraction standard set; calculated provisional standard 525 µg/l	see 8.5
Water intended for human consumption (WIHC)	no EU standard set	see 8.5

3 Classification

CAS No.	Substance	R-Phrases and Labelling	Ref.
1806-26-4	octylphenols	This chemical substance is not classified in the Annex I of Directive 67/548/EEC.	[17]
140-66-9	para-tert octylphenol	This chemical substance is not classified in the Annex I of Directive 67/548/EEC.	[17]
140-66-9	para-tert octylphenol	Agreement on the environmental classification of 4-*tert*-octylphenol according to Directive 67/548/EEC was reached at an EU expert meeting in September 2004. The substance is classified as 'dangerous to the environment' with the following risk phrase: R50/53 This classification is the same as the provisional classification included on manufacturer's Safety Data Sheets (Aldrich Chemicals, 2002; SASOL, 2001). The human health classification is not considered in this assessment.	[15]

4 Physical and chemical properties

Property	Value	Ref.	Comments
Mol. Weight:	206.33 g/mol	[5]	
Water Solubility	5 mg/l 25° C 12.6 mg/L (20,5 °C)	[6] [5]	
Vapour Pressure:	64 mPa 4.7 Pa 74°C	[6]	
Henry Constant	0.699 Pa m^3/mol (20° C)	[6]	
Dissociation constant:			

5 Environmental fate and partitioning

Property	Value	Ref.
Abiotic degradation Hydrolysis Photolysis	In the atmospheric compartment, degradation of 4-*tert*-octylphenol through reactions with hydroxyl radicals is rapid, with an estimated half-life of 0.25 days. Abiotic degradation processes in water are likely to be negligible.	[9]
Biodegradation	Substance biodegradable under aerobic and anaerobic conditions. Inherently biodegradable, >60% (35d) in mod. Sturm-test (OECD 301B) but failing 10d window criterion. A biodegradation study carried out to GLP and OECD test guidelines together with a laboratory microcosm study suggest that 4-*tert*-octylphenol is inherently degradable, although micro-organisms may need a period of adaptation. A study on degradation in river waters and sediments suggested that biodegradation half-lives were generally shorter in more urban/industrialised areas suggesting that some form of acclimation may occur. However, the same study showed that there was no degradation in anaerobic bed sediments.	[6] [1] [9]
Partition coefficients log Kow Koc 	 5.3 4.5 >3 - 3.7 3.96 4.12 log Koc 4.3 3500 – 18500 L/kg (sediment) 2740	 [6] [1] [7] [5] [9] [6] [5] [9]
Bioaccumulation BCF Oncorhynchus mykiss Fish	 6000 2291 (calculated) 471 (10 d) The calculated fish BCF of 634 is used in the risk assessment as a reasonable worst case. *(The limited measured data from fish studies suggest that the potential for bioaccumulation in aquatic organisms will be low to moderate [15])*	 [6] [1] [5] [15]

6 Effect data (aquatic environment)

All aquatic toxicity data collated in this data sheet that have been provided by France [6] or by Germany [1, 5] refer to para-tert-octylphenol (CAS No. 140-66-9). The data submitted by the United Kingdom [7] are for octylphenols (CAS No. 27193-28-8) or para-tert-octylphenol [9, 15]. However, the CAS number of the octylphenols for which the quality standard is to be derived is 1806-26-4. It is not clear what the difference is between the octylphenols of CAS Nos. 27193-28-8 and 1806-26-4 (or whether there is a difference at all). As all substances subsumed under the different CAS numbers have the same molecular weight and as all octylphenols are assumed to be similar in toxicity [8], no differentiation between the individual substances has been made in this data sheet[1].

The quality standards proposed in section 8 of this data sheet are based on the data evaluated and the effect assessments conducted in the context of the risk evaluation of 4-tert-octylphenol commissioned by the United Kingdom Environment Agency [9, 15].

6.1 Mode of action of octylphenols

The following text is an abridged adaptation of section 4.5 of the OP-RAR [15].

4-tert-Octylphenol may exert its effects on organisms by more than one mode of action. The substance falls into the category of polar narcotics as defined by OECD toxicity classes. However, this classification does not provide an indication of the actual mode of toxic action at a cellular level, and a number of mechanisms could be operating to disrupt cellular function and produce toxicity. The standard toxicity data do not provide any indication of exactly which systems are being affected.

Endocrine-mediated responses, on the other hand, are most likely to be mediated by a specific mechanism, and the majority of the data for this substance point towards interference and/or competition with the binding of natural oestrogens (such as 17β-estradiol) to receptor sites and mimicry of their effects (i.e., an oestrogen agonist). There are some structural similarities between 4-tert-octylphenol and certain hormones, and 4-tert-octylphenol has been demonstrated to bind to the oestrogen receptor in almost exactly the same way as estradiol.

There are also indications that 4-tert-octylphenol may act as an anti-androgen, by displacing androgen from the androgen receptor. There are, however, other possible non receptor-mediated modes of action for the endocrine disruption effects reported, some of which may also be important in the more general toxicity seen. These mechanisms include calcium-dependent apoptosis, and also inhibition of the testicular calcium ATPase enzyme (leading to disruption of testicular development and a decrease in fertility). One cellular mechanism reported in a number of recent articles involves the disruption of cytochrome P450 enzymes, which has consequential effects on steroidogenesis – this could potentially produce effects on the endocrine system.

There are insufficient data to adequately describe a definitive mechanism of action for either general toxicity or endocrine effects for 4-tert-octylphenol, but it is possible that more than one may be acting, and that the two types of effects may be linked.

[1] see also table 6.1. No obvious difference in toxicity between para-tert- octylphenol (CAS 140-66-9) and octylphenol (CAS 27193-28-8) can be seen.

Table 6.1 Summary on endocrine disrupting potential of octylphenols

CAS No.	Name		Reference
1806-26-4	Octylphenols	substance not mentioned in [2]	[2]
27193-28-8	Octylphenols	substance not mentioned in [2]	[2]
140-66-9	(para-tert-octylphenol)	substance with evidence of ED or evidence of potential ED	[2]
140-66-9	(para-tert-octylphenol)	Overall on the basis of the valid studies the lowest NOEC for endocrine modulation of reproductive performance in aquatic organisms is 12 μg/l, based on the data from the Wenzel *et al* (2001) study with fish. However, effects on VTG production in rainbow trout (*Oncorhynchus mykiss*) have been observed at 1.6 μg/l. Furthermore, data from studies (of use with care status) in molluscs and amphibians indicate that a lower NOEC, potentially less than 1 μg/l, may be appropriate. These data cannot reasonably be used at present without further more reliable evidence to support them, but may indicate a need for further testing. This will be considered in the PNEC derivation and risk characterisation.	[9]

6.2 Toxicity of octylphenol observed for traditional endpoints (effects not caused by interference of OP with the endocrine system)

The toxicity data for 4-*tert*-octylphenol considered most relevant in the RAR [15] are summarised in tables 6.2 (aquatic toxicity data) and 6.4 (mammalian and bird oral toxicity data relevant for the assessment of secondary poisoning).

The most sensitive trophic levels based on freshwater data would appear to be aquatic invertebrates and fish. Overall, the lowest valid long-term NOEC value was 6.1 µg/L for growth inhibition in rainbow trout (*On. mykiss*) fry after 60 days exposure, with a corresponding LOEC value of 11 µg/L. There is a possibility that effects on the endocrine system may have caused the observed toxicity. Note that the acute toxicity result for *G. pulex*, an EC50 of 13.3 µg/L, is only a little higher than the fish NOEC. This may indicate a higher sensitivity for some invertebrates.

6.3 Toxicity of octylphenol exerted by its capability to interfere with endocrine regulation

The following text is an abridged adaptation of sections 4.1.6.1 & 4.1.6.4 of the OP-RAR [15].

Alkylphenols are known to act as weak oestrogens in fish, and so might cause effects on endocrine systems that are not identified by the usual 'base set' tests. The validity of the available data was assessed in the RAR [15] in a similar manner to that for standardised toxicity endpoints. The key issues remained whether a valid experimental design was adopted, the number of exposure concentrations and the interval between them, whether exposure concentrations were analytically confirmed and the statistical treatment of the data.

When examining the various endpoints from studies that investigated endocrine mediated responses in wildlife species it is important to try to consider their ecological significance. It can be argued that any irreversible physiological or histological change following exposure to a chemical (which is outside normal background limits) is inherently adverse and should be avoided, especially if it can be linked mechanistically with anatomical or physiological effects. However, it may be more appropriate to try to protect against effects related to reproductive activity and sexual development. In terms of protecting the environment, population sustainability is the ultimate goal and thus any adverse effect that may provoke population declines is of particular relevance. Hence

a key issue must be the ability for males and females of species to breed and produce viable offspring that can develop and then successfully reproduce. [15]

In the aquatic environment the lowest NOEC from a valid study assessing the endocrine disrupting effects in fish was 1.6 µg/L for VTG induction in adult male rainbow trout (*On. mykiss*) after 21 days exposure to 4-*tert*-octylphenol (Jobling *et al.* 1996 [20]). Routledge *et al.* (1998) [29] reported a NOEC of 10 µg/L for VTG induction in the same species and with the same exposure duration. The reason for this difference is not clear, but may result from the different times of year at which the studies were conducted. In other species higher concentrations of 4-*tert*-octylphenol have been required to elicit VTG induction. While induction of VTG is recognised as a valuable biomarker of exposure of fish to oestrogenic substances, its relationship with regard to reproductive output and development has not been established clearly.

Wenzel *et al.* (2001) [34] in a life-cycle study with zebrafish (*Da. rerio*) reported a NOEC of 12 µg/L (based on measured concentrations) for a range of endpoints affecting the reproductive success of fish that had been exposed to 4-*tert*-octylphenol from the fertilised egg stage. The endpoints were: time to first spawning, total number of eggs per female and day, fertilisation capacity and the cumulative number of fertilised eggs. All these parameters were significantly affected at an exposure concentration of 35 µg/L. Segner *et al*. (2003) [30] reported a lifetime exposure study on the same species, from which an EC50 of 28 µg/L was determined. They considered that this was the reproduction parameter affected most consistently and reproducibly. A valid study by Van den Belt *et al.* (2001) [33], in which adult male and female zebrafish were exposed to 4-*tert*-octylphenol for 3 weeks, showed no effects on spawning ability even at a concentration of 100 µg/L. These data, while initially appearing contradictory, indicate that there are probably differences in species sensitivity to 4-*tert*-octylphenol in terms of endocrine-mediated responses and that the critical window of exposure for the effects on reproduction may be during the early life stage of the fish.

In a valid study of reproductive impairment in adult male Japanese medaka (*O. latipes*), Gronen *et al.* (1999) [19] found that breeding groups composed of exposed males (at 20 µg/L for 3 weeks) and control females produced about 50% fewer eggs than control groups. Significant increases in abnormal embryos produced by unexposed females mated with exposed males (at 20 µg/L) were also evident. These data once again indicate that, as might be expected, there are probably differences in species sensitivity to 4-*tert*octylphenol in terms of endocrine-mediated responses.

Knörr and Braunbeck (2002) [24] reported similar results in Japanese medaka. When exposed males were mated with control females, increased mortality was seen at 20 µg/L. When exposed females were mated with control males, the increase in mortality was not seen until 50 µg/L. Mortality was not increased at 2 µg/L, which could be taken as a NOEC for mortality (although there is a factor of 10 between the concentrations). Other endpoints in the same study indicated significant changes at 20 µg/L, with smaller effects at 2 µg/L.

Seki *et al*. (2003) [31] observed testis-ova in medaka exposed to concentrations of 4-*tert*octylphenol of 11.4 µg/L and above, with increases in VTG at the same concentrations. The NOEC from this study was 6.94 µg/L.

In a study on the guppy (*Po. reticulata*), a number of parameters, including mortality, male colouration, GSI in females and sexual behaviour, were all affected at 149 µg/L but not at 11.7 µg/L (Toft and Baatrup, 2003) [32]. The separation between these concentrations is large. Mortality of embryos in the viviparous fish eelpout (*Z. viviparus*) was increased following exposure of pregnant female fish to 64 µg/L, and the development (weight and length) of the embryos was reduced at 14 µg/L (Rasmussen *et al.*, 2002) [28].

In the estuarine fish sheepshead minnow (*C. variegatus*) abnormalities in the testes were observed at 33.6 µg/L, but not at 11.5 µg/L (Karels *et al*., 2003) [22]. VTG levels were elevated at both concentrations.

For amphibians, a study by Kloas *et al.* (1999) [23] reported a NOEC of 2.1 µg/L for effects on sex ratios in *X. laevis* exposed to 4-*tert*-octylphenol for 84 days from 2-3-day-old posthatch larvae. However, it needs to be recognised that this study was not carried out to a standard regulatory test protocol and the data need to be considered in this context. The findings of a similar study on bisphenol-A could not be reproduced in a repeat study by a different laboratory, and the study is therefore classed as 'use with care'.

Changes in the development of the bullfrog (*R. catesbeiana*) were observed by Mayer *et al*. (2003) [26]. The stage at which sexual differentiation was completed in tadpoles was advanced by exposure to 0.2 µg/L and above. The significance of this change is not clear, and there were no changes to the sex ratios.

For invertebrates, a study by Oehlmann *et al.* (2000) [27] (with a 'use with care' status) showed significant effects on the reproductive anatomy of freshwater (*Ma. cornuarietis*) and marine (*N. lapillus*) prosobranch snails. In experiments with *Ma. Cornuarietis*, octylphenol induced a complex syndrome of alterations in females (referred to as 'superfemales') at the lowest concentration of 1 µg/L. Since statistically significant effects were observed at the lowest nominal test concentrations (1 µg/L), the authors concluded that even lower concentrations may have a negative impact on the snails. As with the amphibian study, this test was not carried out to a standard regulatory test protocol and the data need to be considered in this context.

Studies on another snail species *Ps. antipodarum*, showed an increase in embryo production, significant at 5 µg/L but not at 1 µg/L (Jobling *et al*., 2003) [21]. In the estuarine copepod *Tigriopus japonicus*, delays in the completion of the naupliar stage in the F1 generation were observed at concentrations down to 0.01 µg/L (Marcial *et al*., 2003) [25]. However, the authors concluded that exposures at up to 10 µg/L would have little impact on the demographic profile of the species. An EC10 of 5.2 µg/L was determined by Andersen *et al*. (2001) [18] for the marine copepod *A. tonsa*, also for delay in naupliar development.

Overall, on the basis of the fully *valid* studies, the lowest NOEC for endocrine modulation of reproductive performance in aquatic organisms is 12 µg/L, based on the data from the Wenzel *et al.* (2001) [34] study with fish. However, effects on VTG production in rainbow trout (*On. mykiss*) have been observed at concentrations above 1.6 µg/L. Furthermore, data from studies (of use with care status) in molluscs and amphibians indicate that a lower NOEC, potentially less than 1 µg/L, may be appropriate. In the RAR [15] the opinon is expressed that these data are difficult to use in the risk assessment at present, and would benefit from further, more reliable, evidence to support them (i.e., there may be a need for further testing).

Table 6.2 Summary of valid traditional endpoint toxicity data used to derive the aquatic PNEC of octylphenol in the RAR [15] and comparison with respective data of nonylphenol

Data type		4-tert-octylphenol	Nonylphenol
Acute fish (freshwater)	96-hour LC50 Fathead minnow *Pimephales promelas*	290	128
	6-day LC50 Rainbow trout *Onocrhynchus mykiss*	170	-
Chronic fish (freshwater)	60-day $NOEC_{growth}$, Rainbow trout *Onocrhynchus mykiss*	6.1	-
	33-day NOEC survival Fathead minnow *Pimephales promelas*	-	7.4
Acute fish (saltwater	96 hour LC50 Killifish *Fundulus heteroclitus*	280 – 340 (use with care)	-
	96-hour LC50 Sheeptshead minnow *Cyprinodon variegatus*	720 (use with care, 72 h)	310
Chronic fish (saltwater)	-	-	-
Acute invertebrates (freshwater)	4h-hour EC50 *Daphnia magna*	270	85
	96-hour EC50 *Gammarus pulex*	13.3	12.7
Chronic invertebrates (freshwater)	21-day NOEC surviving offspring *Daphnia magna*	62	24
Acute invertebrates (saltwater)	96-hour growth *Mysidopsis bahia*	53.4 (use with care)	43
	48-hour LC50 Arcartia tonsa	420	-
Chronic invertebrates (saltwater)	28-day NOEC survival *Mysidopsis bahia*	-	3.9
Algae (freshwater)	72-hour EC10 growth rate *Scenedesmus subspicatus*	300 (use with care)	25.1 or 500
	72-hour EC50 growth rate *Scenedesmus subspicatus*	1100 (use with care)	323 or 1300
Algae (saltwater)	96-hour EC50 cell growth *Skeletonema costatum*	-	27

Comparison with nonylphenol [15]

Nonylphenol has a much larger toxicity dataset and it is useful to compare this with the data for 4-tert-octylphenol, to test the potential for read-across. Table 4.5 lists data for the same trophic levels and species (where available) for each substance. For comparative purposes, the toxicity should be expressed on a molar basis, but since nonylphenol is not a pure substance, this is not considered essential in this case. In general the substances show similar toxicity for a particular taxonomic group (algae, invertebrates and fish) and test type (i.e., acute or chronic). In most cases the toxicity values are within a factor of three of one another. The major difference occurs for algal toxicity. For nonylphenol, the lowest chronic algal value was a 72-hour EC10 of 3.3 µg/L for biomass inhibition in S. subspicatus. There are no fully valid algal data for 4-tertoctylphenol, and no data for biomass inhibition to compare against the nonylphenol results. However, the biomass end point is no longer preferred for PNEC derivation. In fact, invertebrates and fish are both more sensitive than algae for both alkylphenols when algal growth rate is used (i.e., the profile is the same). In addition, other results were available for the same algal species for nonylphenol, and these were very similar to those obtained for 4-tert-octylphenol. Comparisons with QSARs for phenols (see Section 4.1.4) show that both the short- and longer-term predicted algal toxicity values are broadly similar to those measured in the 'use with care' studies (see Table 4.3). The use of the nonylphenol algal biomass EC10 was, however, supported by a 28-day NOEC for survival in M. bahia of 3.9 µg/L. Since there are no comparative chronic M. bahia data available for 4-tert-octylphenol, it is possible that this could be an important data gap. From the information available, it does not seem likely that 4-tert-octylphenol and nonylphenol exert their effects through different modes of action given the structural similarities between the substances. It may, therefore, be important to obtain further chronic invertebrate toxicity data for 4-tert-octylphenol in any refinement of the risk assessment. This is considered further in the risk characterisation (Section 5). Valid saltwater species toxicity data for 4-tert-octylphenol were limited to acute data for invertebrates. Comparison of the 48-hour lethality data for freshwater and saltwater crustacean species suggests that sensitivity is similar with a 48-hour LC50 value of 270 µg/L for D. magna and a 48-hour LC50 value of 420 µg/L for A. tonsa. Values for acute fish toxicity tests were also comparable, although the data for the estuarine fish F. heteroclitus and for C. variegatus were from 'use with care' studies.

Table 6.3: Overview on toxicity data of most sensitive species from different sources (master reference).

Subs-tance *	Species	Taxonomic Group	Duration	Effect	Endpoint	Value µg/l	Master reference	Reference in master reference	Comments on data reliability in master reference
	Freshwater								
P	Oncorhynchus mykiss	Pisces	108 d	Weight	NOEC	1	[5]	Ashfield et al. 1998	Not used for PNEC derivation in UK- OP-RAR[#]
P	Oncorhynchus mykiss	Pisces	21 d	Vitellogenin production	EC0	1-10	[5]	Routledge et al. 1998	In UK OP-RAR considered as valid but not directly used for PNEC derivation [##]
P	Oncorhynchus mykiss	Pisces	21 d	Vitellogenin production	NOEC	1.6	[5]	PSM-Datenbank 1995 Harries et al.	
P	Oncorhynchus mykiss	Pisces	21 d	Sperma development	EC0	1.8	[5]	Jobling et al. 1996	
P	Oncorhynchus mykiss	Pisces	21 d	Vitellogenin production	EC0	4.8	[5]	Jobling et al. 1996	In UK OP-RAR considered as valid but not directly used for PNEC derivation [##]
O	Oncorhynchus mykiss	Pisces	60 d	ELS post hatch	NOEC LOEC	6.1 11	[7]	IUCLID (1996)	GLP
P	Rutilus rutilus	Pisces	21 d	Vitellogenin production	EC0	10	[5]	Routledge et al. 1998	In UK OP-RAR considered as valid but not directly used for PNEC derivation [##]
P	Daphnia magna	Crustacea	21 d		EC0	24	[5]	Staples et al. 1998	
O	Daphnia magna	Crustacea	21 d	reproduction	NOEC LOEC	30 100	[7]	IUCLID (1996)	Lower Daphnia value
P	Daphnia magna	Crustacea	21 d		NOEC	37	[5]	Staples et al. 1998	
P	Chironomus tentans	Insecta	14 d		NOEC	39 – 143	[5]	Staples et al. 1998	
O	Scenedesmus subspicatus	Algae	72 h	growth	EC10	300	[7]	IUCLID (1996)	
O	Gammarus pulex	Crustacea	96 h	immobilisation	EC50	13.3	[7]	Sims and Whitehouse (1998)	GLP
P	Acute toxicity daphnia	Crustacea				30	[1]	IuclidAquatox	
P	Daphnia magna	Crustacea	48 h		LC50	90	[6]	Zou and Fingerman 1997	
O	Daphnia magna	Crustacea	24 h	mortality	LC50	170	[7]	IUCLID (1996)	Lowest Daphnia value
O	Pimephales promelas	Pisces	96 h	mortality	LC50	250	[7]	IUCLID (1996)	GLP
P	Acute toxicity fish	Pisces				260	[1]	IuclidAquatox	
O	Daphnia magna	Crustacea	48 h	mortality	LC50	270	[7]	IUCLID (1996)	Highest Daphnia value
P	Fundulus heteroclitus	Pisces	96 h		LC50	285	[6]	Kelly and Di Guilio 2000	
P	Oryzias latipes	Pisces	17 d		LC50	450	[6]	Gray and Metcalfe 1999	
O	Daphnia magna	Crustacea	21 d		EC50	340	[7]	IUCLID (1996)	GLP; Upper Daphnia value

Subs-tance *	Species	Taxonomic Group	Duration	Effect	Endpoint	Value µg/l	Master reference	Reference in master reference	Comments on data reliability in master reference
P	Acute toxicity algae	Algae				1100	[1]	IuclidAquatox	
P	Selenastrum capricornutum	Algae	96 h		EC50	1900	[6]	EPA 1984	
P	Selenastrum capricornutum	Algae	96 h		EC50	1900	[5]	Staples et al. 1998	
	Seawater								
O	Mysidopsis bahia	Crustacea	96 h	mortality	LC50	47.9-113.1	[7]	Cripe et al (1989)	The range is dependent on food availability
O	Crangon septemspinosa	Crustacea	96 h	mortality	LC50	1100	[7]	Mcleese et al (1981_	

* P = para-tert-octylphenol (CAS No. 140-66-9); O = Octylphenols (CAS No. 27193-28-8)

\# In the OP-RA carried out by UK [9] the study by Ashfield et al. was rated as "use with care" because the nominal exposure concentrations were not confirmed analytically. Further, the absence of a concentration-response relationship for body weight over the two exposure regimes complicates the interpretation of the data and means that the significance of the effect at 1 µg/l is uncertain. Therefore, the study was not used to derive the PNEC in the OP-RA.

\## In UK OP-RA [9] not directly used because the ecological significance of the observed effects is not clear. Citation from the draft OP-RAR (section 4.1.6.4): *"In the aquatic environment the lowest NOEC from a valid study assessing the endocrine disrupting effects in fish was 1.6 µg/l for VTG induction in adult male rainbow trout (Oncorhynchus mykiss) after 21 days exposure to 4-tert-octylphenol (Jobling et al 1996). A NOEC of 10 µg/l for VTG induction in the same species and with the same exposure duration was also reported by Routledge et al (1998). The reason for this difference is not clear but may reflect differences in the sensitivity of the measurement technique between the two studies. In other species higher concentrations of 4-tert-octylphenol have been required to elicit VTG induction. While induction of vitellogenin is recognised as a valuable biomarker of exposure of fish to estrogenic substances, its relationship with regard to reproductive output and development has not been clearly established."…"Overall on the basis of the valid studies the lowest NOEC for endocrine modulation of reproductive performance in aquatic organisms is 12 µg/l, based on the data from the Wenzel et al (2001) study with fish. However, effects on VTG production in rainbow trout (Oncorhynchus mykiss) have been observed at 1.6 µg/l. Furthermore, data from studies (of use with care status) in molluscs and amphibians indicate that a lower NOEC, potentially less than 1 µg/l, may be appropriate. These data cannot reasonably be used at present without further more reliable evidence to support them, but may indicate a need for further testing. This will be considered in the PNEC derivation and risk characterisation."*

Table 6.4: Mammal and bird oral toxicity data relevant for the assessment of non compartment specific effects relevant for the food chain (secondary poisoning) [9, 15]

Test species	Exposure period	Test concentration series used	Endpoint	Effect concentration	Reference
Male and female rats (Wistar)	90 days	0, 30, 300 and 3000 ppm day^{-1}	NOEL LOEL	30 ppm 300 ppm	SIDS 1994
Male and female rats (CD: Sprague-Dawley strain)	28 days	0, 15, 70 and 300 mg kg bw^{-1} day^{-1}	NOEL LOEL	15 mg kg^{-1} bw day^{-1} not given	SIDS 1994
Male and female albino rats (Sprague-Dawley strain)	29 days	0, 15, 150 and 250 mg kg bw^{-1} day^{-1}	NOEL LOEL	15 mg kg^{-1} bw day^{-1} 150 mg kg^{-1} bw day^{-1}	SIDS 1994
Male and female CD rats *	2 genera-tions	0.015, 1.5, 15 and 150 mg/kg bw/day	NOAEL	15 mg kg^{-1} bw day^{-1}	Tyl et al. 1999 [13]

* see description in section 7 for further details

7 Effect data (human health)

To determine the potential reproductive toxicity of octylphenol, a two-generation reproduction study was conducted according to U.S. EPA OPPTS Guideline 870.3800 (draft 1996). Additional measurements were made on retained F2 offspring. OP was administered *ad libitum* to five groups of rats (30/sex) at dietary concentrations of 0, 0.2, 20, 200, or 2000 ppm. The 0.2 ppm concentration was included to evaluate potential low dose effects. Effects were observed only at 2000 ppm, including decreased body weights in adults and during the latter portion of lactation in offspring and minor body weight-related delays in acquisition of vaginal opening and preputial separation. No effects on reproductive parameters, testes, prostate, or ovary weights or morphology, on sperm counts, motility, morphology, production, or on estrous cyclicity were observed. No estrogen-like effects were evident. The NOAELs for systemic and postnatal toxicity were 200 ppm and at or above 2000 ppm for reproductive toxicity [13]. These NOAELs are equivalent to doses of 15 mg/kg bw/d and 150 mg/kg bw/d, respectively [12].

Following sub-cutaneous injections of doses of 4-tert octylphenol of 30 mg kg^{-1} body $weight^{-1}$, histopathological effects have been found on the testis and hormone levels in male and female rats. The changes were statistically significant but the longer-term biological consequences of the histological effects is not certain given the absence of such responses in the two generation study in rats [12].

NO(A)ELs of 15-30 mg kg body weight-1 day^{-1} have been reported for general systemic effects in mammals following exposure to 4-tert octylphenol. As a result it appears that endocrine mediated responses may be among a number of mechanisms responsible for the most toxic effects observed [12].

OP is rapidly metabolised and eliminated in mammals; oral bioavailability is low, OP is unlikely to bioaccumulate in mammalian species [1]; no indications for bioaccumulation have been observed in a 2-generation reproductive toxicity study in rats [14].

8 Calculation of quality standards

8.1 Quality standards for water

Freshwater

A summary of aquatic toxicity data for octylphenols is provided in tables 6.2 & 6.3.

The data considered most reliable in the OP-RA carried out by UK [15] are summarised in table 6.2. Conclusion of the RAR is that for this substance, valid short- and long-term data are available for freshwater invertebrates and fish but not green algae (the available algal studies all have a "use with care" status).

Of the data collated in table 6.2 for 'traditional' toxicity endpoints, the NOEC (growth) of 6.1 µg/l from the 60-day post-hatch early life stage toxicity study with rainbow trout (*Oncorhynchus mykiss*) is considered the most relevant value for use in the PNEC derivation. Nevertheless it is noted that the invertebrate *Gammarus pulex* is more sensitive in acute tests than other organisms, and a chronic NOEC is not available for this species. The RAR states further that there is also evidence from nonylphenol that invertebrates (and possibly algae) are more sensitive than fish in chronic tests. Therefore, an assessment factor of 50 is identified as appropriate in the RAR. This results in a PNEC of 0.122 µg/l.

Consideration of 'endocrine disruption' data [15]

On the basis of valid studies, the lowest most relevant NOEC for endocrine-mediated responses in aquatic organisms is 12 µg/L from a life-cycle study with the zebrafish *Brachydanio rerio* (Wenzel et al., 2001). This is higher than the lowest NOEC (growth) for general ecotoxicological effects of 6.1 µg/L from the 60-day post-hatch early life stage toxicity study with the rainbow trout *Oncorhynchus mykiss*.

However, effects on VTG production in rainbow trout have been observed at concentrations above 1.6 µg/L, which is the lowest NOEC value for fish. There are also NOEC values of 11.7 µg/L for the guppy, 6.94 µg/L for the medaka and 11.5 µg/L for the sheepshead minnow. In addition, data from studies (of 'use with care' status) in molluscs and amphibians suggest that a lower NOEC – potentially less than 1 µg/L – may be appropriate for these organisms. A possible NOEC of 1 µg/L is indicated for *Ps. antipodarum*. Changes in the development of bullfrog tadpoles were observed at 0.2 µg/L, but the significance of these is not clear. Delays in the completion of the naupliar stage in marine copepods were observed at 0.01 µg/L, but the authors considered these would have little impact on the demographic profile of the organism at concentrations up to 10 µg/L. The PNEC from the 'standard' toxicity test results is lower than all of the above values, with the exception of that for copepods. Neglecting this exception in light of the authors' comments, there is a margin of around eight-fold between the PNEC and the level at which effects seen in snails, and less than double for bullfrogs (but with no indication of the significance or otherwise of this effect). Although a second PNEC could be derived from the data, the choice of concentration to use (as some are effects at the lowest tested concentration) and assessment factor would be somewhat arbitrary. Instead, the risk characterisation considers which endpoints would give a margin of safety of 10 based on the data above.

Based on the above considerations on the endocrine disrupting potential of 4-tert-octylphenol it is concluded in the RAR that the PNEC derived on the basis of the conventional toxicological endpoints (i.e. non ED-mediated toxicity of OP) provides a sufficient margin of safety against potential ED-mediated effects of 4-tert-octylphenol.

It is suggested to agree with the conclusion drawn in the RAR and to derive the quality standard referring to the protection of the pelagic community in freshwater on the basis of the NOEC (growth) of 6.1 µg/l from the 60-day post-hatch early life stage toxicity study with rainbow trout (*Oncorhynchus mykiss*) and an assessment factor of 50:

$QS_{freshwater}$ = 6.1 µg/l / AF (50) = 0.122 µg Octylphenol/l

Koc values between approximately 3,500 and 19,950 have been reported (see section 5 of this data sheet). Hence, the log Kp_{susp}[2] is between 2.54 and 3.3. Given the high water solubility of octylphenols it appears not sensible to monitor the compound in suspended particulate matter. Therefore a concentration in SPM corresponding to the QS_{water} is not calculated.

Transitional, coastal and territorial waters

For 4-*tert*-octylphenol there are valid acute saltwater data for invertebrates (*Arcartia tonsa*, LC50 420 µg/l) and fish (*Fundulus heteroclitus* LC50 280-340 µg/l & *Cyprinodon variegatus* LC50 720 µg/l) available (tab. 6.2).

However, no long-term NOEC values are available for saltwater species. The lowest valid long-term NOEC for a freshwater species is 6.1 µg/L for the growth of rainbow trout (*On. mykiss*). Long-term NOECs are also available for algae (based on growth in *Scenedesmus subspicatus* and *Selenastrum capricornutum, but with "use with care" status*) and invertebrates (juvenile production in *D. magna*), but these values are higher. The database has no representatives from additional marine taxonomic groups. As there are valid long-term NOEC values for only two different taxonomic groups, a factor of 500 could be considered. The arguments regarding the sensitivity of invertebrates not represented in the long-term data presented for the freshwater QS (section 8.1) are also applicable here. In particular, for nonylphenol there are results with saltwater invertebrates that show lower effect levels. From the tests to look at endocrine-disrupting effects, there are NOEC values for the sheepshead minnow of 11.5 µg/L, and for the sand goby of 7 µg/L. The saltwater copepod *Tigriopus* showed effects at 1 µg/L in a long-term study, although the authors considered that exposure at the levels tested (up to 10 µg/L) would have little impact on the population. The data on saltwater organisms is limited, and is not considered sufficient to allow a reduction of the assessment factor of 500.

$QS_{saltwater}$ = 6.1 µg/l / AF (500) = 0.0122 µg Octylphenols/l

This saltwater QS covers the observed endocrine effects of octylphenol on the most sensitive group of gastropods with an appropriate margin of safety. At the current state of knowledge, it is therefore not deemed necessary to lower this QS further.

Quality standard accounting for transient concentration peaks (MAC-QS)

It is suggested to derive the MAC-QS on the basis of the lowest acute toxicity test available. An EC50 of 13.3 µg/l (immobilisation) has been obtained for the crustacean species *Gammarus pulex* (see table 6.2).

Based on the guidance given in the TGD on the effects assessment for intermittent releases (section 3.3.2 of part II of [3]) it is suggested to apply an assessment factor of 100 in order to derive the MAC-QS.

[2] Kp_{susp} is the partition coefficient solid-water in suspended matter = Koc * foc (with foc 0.1; see TGD section 2.3.5.3 [3]).

MAC-QS = 13.3 µg/l / AF (100) = 0.133 µg Octylphenols /l

8.2 Quality standard for sediment

Koc values between approximately 3,500 and 19,950 have been reported (see section 5 of this data sheet). Hence, the log Kp_{susp} is between 2.54 and 3.3 (see footnote 2). Hence, the trigger for the derivation of a sediment quality standard is met, although not unequivocally.

The only test result found for exposure of organisms via sediment is the study on *Ps. antipodarum* described in section 4.1.6.3.1 of the RAR [15]. In this study there were increases in the number of unshelled embryos relative to controls at 4 weeks at all concentrations used (the lowest was 1 µg/kg dw), and in the total numbers of embryos at concentrations of 30 µg/kg dw and above. As effects were seen at all concentrations, no NOEC value can be derived from the study. The data at 4 weeks allowed for a non-linear regression analysis that gave estimates of the EC10 value for stimulation of embryo production, 4 ng/kg for unshelled embryos and 2.1 µg/kg for total embryos. The data at 2 and 8 weeks did not allow a similar analysis. The value for unshelled embryos is extrapolated over two orders of magnitude below the lowest (nominal) exposure level and as such has a high degree of uncertainty. The production of additional embryos is considered to be a potentially harmful effect, as it involves the use of energy resources in the organism out of the normal embryo production period, and also the release of young into the environment at possibly less than optimum times. However, it is not clear whether the numbers of new unshelled embryos or the total embryos should be used as a parameter for this effect, and it is not considered possible at present to determine a reliable no-effect level from this study.

No valid toxicity data are available for sediment-dwelling species for 4-*tert*-octylphenol [15]. In this case, accordance with the agreed methodological framework for the derivation of quality standards [4] and the TGD [3], the $QS_{sediment}$ may be calculated using the equilibrium partitioning method.

The equilibrium partitioning approach only considers uptake via the water phase. However, uptake may also occur via other exposure pathways like ingestion of sediment and direct contact with sediment. There is evidence from studies in soil that the proportion of the total dose remains low for chemicals with a log Kow up to 5. As the log Kow of octylphenol is reported in most references to be <5, in the OP-RAR 4.12 (see section 5 of this data sheet), exposure routes other than direct uptake via the water phase need not to be considered and the $QS_{sediment}$ is calculated as follows:

$$QS_{sed.wet\_weight}\ [mg.kg^{-1}] = \frac{Kp_{SPM\text{-}water}\ [69.4\ m^3/m^3]}{bulk\ density_{SPM.wet}\ [1150\ kg/m^3]} * 1000 * QS_{water}\ [mg/l]$$

with:

$K_{SPM\text{-}water}$ [3] = f_{water} (0.9) + f_{solid} (0.1) * Kp_{susp} (274 l/kg) / 1000 * RHO_{solid} (2500 kg/m^3) = 69.4 m^3/m^3

bulk $density_{SPM.wet}$ = 1150 kg/m^3

1000 = conversion factor m^3/kg to l/kg

$QS_{freshwater}$ = 0.000122 µg/l

$QS_{saltwater}$ = 0.0000122 µg/l

The TGD defines wet SPM as 90% vol/vol water (density 1 kg/l) and 10% vol/vol solids (density 2.5 kg/l), thus giving a wet density of (0.9 × 1) + (0.1 × 2.5) = 1.15 kg/l. The dry weight of solids is therefore 0.25 kg (per litre wet SPM) and thus the wet:dry ratio is 1.15/0.25 = 4.6.

[3] It is proposed to use the Koc identified in the draft OP-RAR [9] as appropriate (2740) for the calculation of the $Kp_{SPM\text{-}water}$. Kp_{susp} = Koc * foc = 2740 * 0.1 = 274

This results in the following quality standards for sediment (wet and dry weight):

$QS_{sediment.freshwater}$	7.4 µg/kg (wet wt)	34 µg/kg (dry wt)
$QS_{sediment.saltwater}$	0.74 µg/kg (wet wt)	3.4 µg/kg (dry wt)

The equilibrium partition result is of the same order as the estimated EC10 value for total embryo production in *Potamopyrgus*, but as the derivation of the aquatic PNEC from which it is calculated includes an assessment factor of 50, the effective no-effect level is higher. This provides additional evidence that snails might be especially sensitive to the effects of 4-*tert*-octylphenol. However, it is difficult to derive a suitable no-effect level from the currently available test results on snails for both sediment and water. The EC10 value for unshelled embryo production is extrapolated too far below the lowest concentration used to be reliable. The value for total embryo production is better defined, but it is not clear if this is the appropriate value to use. [15]

If it should be considered to set a QSsediment on the basis of the currently available data, the lowest concentration tested with snails (at which effects were seen, 1 µg/kg dw) should therefore also considered beside the result of the equilibrium partitioning calculation.

It is however not recommended to set a $QS_{sediment}$ on the basis of the currently available data. In order to derive reliable quality standards for the sediment compartment long term tests conducted with benthic organisms are required.

8.3 Secondary poisoning of top predators

Octylphenols have a BCF >> 100. Thus the trigger criterion to derive a quality standard referring to the protection of top predators from secondary poisoning is met (see table 8.1 of the final report [4]).

Oral toxicity data that could be used to derive a QS referring to secondary poisoning are available from the octylphenol RAR [15]. In the section on the derivation of the $PNEC_{oral}$ (4.4.2) of this report, it is concluded that the most reliable of the available studies is a two-generation study on rats with exposure through food (Tyl *et al*., 1999), which gives a NOAEL of 15 mg/kg/day. This is supported by the results of two shorter (28- or 29-day) oral gavage studies, both of which have NOAEL values of 15 mg/kg/day for relatively minor effects (the next tested levels were 70 mg/kg and 150 mg/kg).

The NOAEL used for the QS derivation is 15 mg/kg/day. The conversion factor to concentration in food is 20 for rats that are more than 6 weeks old, giving a NOEC of 300 mg/kg. As the result is from a chronic study, the appropriate assessment factor is 30, giving a $QS_{secpois.biota}$ of 10 mg/kg in food.

Octylphenol has been shown to be liable to bioconcentration (see section 5 of this data sheet). It is suggested to select the BCF used in the OP-RAR as realistic worst-case (BCF_{fish} 634) to calculate the concentration in water that corresponds to the $QS_{secpois.biota}$.

Information on biomagnification of octylphenol is not available. However, from the information available (see table 6.2) it can be inferred that at least for mammals the risk of biomagnification might be quite low. As the BCF of the substance is <2000, default biomagnification factors need not to be taken into account according to the TGD.

The $QS_{secpois.water}$ is calculated as follows:

$QS_{secpois.water}$ = $QS_{secpois.biota}$ (10 mg/kg prey) / BCF (634) = 15.8 µg Octylphenol /l

Hence, the specific QS required to protect predators from secondary poisoning is lower than the standard derived for the pelagic communities in freshwater and coastal and transitional waters.

8.4 Quality standard referring to food uptake by humans

Octylphenols are not officially classified with respect to possible adverse effects on human health but the manufacturers suggested R-phrases for classification given in the draft UK-RAR on octylphenol [9] comprise the combination R48/22, meaning that the trigger criteria to derive this specific standard were met.

The lowest relevant $NOAEL_{oral}$ identified in the rat reproduction study by Tyl et al. ([13], see section 7) is 15 mg/kg bw d^{-1} for systemic and postnatal toxicity. If the usual assessment factor of 100 is applied to extrapolate from animal to man the $NOAEL_{oral.human}$ is 0.15 mg/kg bw d^{-1} (10.5 mg d^{-1} for a person with 70 kg body weight as relevant threshold level).

In the Manual [4] it is suggested that the relevant threshold level may not be exhausted for more than 10% by consumption of food originating from aquatic sources (i.e. 1 mg d^{-1}).

The average fish consumption of an EU citizen is 115 g d-1 (TGD [3]). Thus, 115 g fish (or fishery products) must not contain more than 1 mg octylphenol.

$$\mathbf{QS_{hh.food}} = \frac{\text{1 mg octylphenol}}{\text{115 g fishery product}} * 1000\ \text{g} = \mathbf{8.7\ mg\ octylphenol\ /\ kg\ fishery\ product}$$

Using the BCF of 634 l/kg identified in the UK risk assessment [9] as reasonable worst-case, a tissue concentration of 8.7 mg octylphenol per kg fishery product results in a water concentration of:

$$\mathbf{QS_{hh.food.water}} = \frac{\text{8.7 mg/kg}}{\text{634 l/kg}} * 1000 = \mathbf{13.7\ \mu g\ octylphenol\ /l}$$

The QS_{water} required to protect the freshwater and saltwater communities are by far lower as the concentrations not to be exceeded in order to protect human health from adverse effects due to ingestion of food from aquatic sources. It is therefore not required to establish a quality standard referring to uptake of food originating from aquatic environments by humans.

8.5 Quality standard for drinking water abstraction

No "A1-value" has been set for drinking water abstraction in Council Directive 75/440/EEC and also no limit value for octylphenols in drinking water applies according to Council Directive 98/83/EC.

Therefore, according to the strategy described in section 4.3.3 of the Manual [4] regarding the derivation of the QS for drinking water abstraction, a provisional drinking water quality standard is to be calculated based on the recommendations given in the TGD.

The lowest relevant $NOAEL_{oral}$ identified in the risk assessment [15] is 15 mg/kg bw d^{-1}. If the usual assessment factor of 100 is applied to extrapolate from animal to man the $NOAEL_{oral.human}$ is 0.15 mg/kg bw d^{-1} (threshold level for human health).

The provisional quality standard for drinking water is calculated with the provision that uptake by drinking water should in any case not exceed 10% of the threshold level for human health [3].

$$QS_{DW.provisional} = \frac{0.1*TL_{HH} * BW}{Uptake_{DW}} = 0.525 \text{ mg octylphenols /l}$$

with:

$QS_{DW.provisional}$	provisional quality standard for drinking water (mg/l)
TL_{HH}	threshold level for human health (0.15 mg octylphenols /kg body weight per day)
BW	body weight (70 kg)
$Uptake_{DW}$	uptake drinking water (2 l per day)

The provisional drinking water quality standard is by far higher than the AA- and MAC- quality standards required to protect the aquatic community. It appears therefore not necessary to derive a quality standard referring to drinking water abstraction as objective of protection.

8.6 Overall quality standard

The quality standards for the protection of the pelagic communities in inland and marine waters are the lowest and are therefore suggested as overall annual average quality standards.

9 References

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